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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,869	02/10/2004	Ekaterina Dadachova	96700/845	1864

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EXAMINER
FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/775,869	Applicant(s) DADACHOVA ET AL.	
	Examiner Brandon J. Fetterolf, PhD	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 June 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-2, 5-19, 25-33, 35-37 and 41-44*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Response to the Amendment

The Amendment filed on 06/27/2006 in response to the previous Non-Final Office Action (02/28/2006) is acknowledged and has been entered..

Claims 1-2, 5-19, 25-33, 35-37 and 41-44 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 1-2, 5-19, 25-33, 35-37 and 41 remain rejected and new claims 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating and/or imaging melanin containing melanoma in a subject comprising administering an amount of a radiolabeled antimelanin antibody, wherein the antimelanin antibody is 6D2, does not reasonably provide enablement for a method of treating and/or imaging any and/or all tumors, including melanoma, comprising administering any and/or all radiolabeled antibodies specific for melanin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-2 read on a method of treating and/or imaging a melanin containing tumor comprising administering a radiolabeled antibody which binds to melanin. Thus, claims 1-4 read a method of treating and/or imaging any and/or all melanin containing tumors comprising administering any and/or all radiolabeled monoclonal or polyclonal antibodies specific for melanin. Claims 5-19, 25-33 and 35-37 read on a method of treating and/or imaging a melanin-containing melanoma comprising administering a radiolabeled antimelanin monoclonal antibody. Thus, the claims read on administration of any and/or all radiolabeled antimelanin antibodies.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a method of treating and/or imaging any and/or all melanin containing tumors, including melanoma comprising administering any and/or all radiolabeled antibodies specific for melanin. The specification teaches (page 5, paragraph 0024) that the present invention involves a method of treating and/or imaging tumors in a subject comprising administering a radiolabeled antibody effective to treat or image the tumor, wherein the antibody binds to a cellular component released by a dying tumor cell including, but not limited to, a histone, a mitochondrial protein, a cytoplasmic protein or a pigment, e.g., melanin. With regards to the tumor, the specification teaches (page 6, paragraph 0030) that the term "tumor" includes melanoma. The specification further provides (page 13, paragraph 0055 to 0056 and page 14, paragraph 0059 to 0060) the in vivo binding/distribution of radiolabeled antimelanin antibody 6D2 in melanoma containing mice, as well as the radioimmunotherapy of melanomas using the radiolabeled antimelanin antibody 6D2. Moreover, the specification provides a prospective example (beginning on page 16, paragraph 0067) on how to make and/or use antibodies to human melanin. Thus, while the specification clearly conveys the treatment and/or imaging of melanin containing melanoma's comprising administering radiolabeled 6D2 anti-melanin antibody, the specification appears to be silent on the treatment of any other tumor or the specificity of any other anti-melanin antibody.

The closest prior art to the instantly claimed invention is Mason et al. (Cancer Research 1954; 14; 648-650), whom teaches a radiolabeled anti-melanin antibody (abstract). Specifically, the

reference teaches that that administration of a radiolabeled anti-melanin antibody to mice bearing melanin containing melanoma's resulted in no significant localization of radioactivity, wherein the failure to localize may be ascribed to several causes, most likely of which is the relative impermeability of mouse melanoma cells to rabbit antibodies (page 650, 1st column, 1st paragraph to 2nd paragraph).

As such, the instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. Those of skill in the art would recognize the unpredictability of using any radiolabeled antibody to melanin for radioimmunotherapy and/or radio imaging. For example, Wilder et al. (J. Clin. Oncol. 1996; 14: 1383-1400) discloses challenges that currently face radioimmunotherapy (abstract). These challenges include: (1) circulating free antigen, biding of antibodies to nonspecific Fc receptors, insufficient tumor penetration, antigenic heterogeneity and insufficient antigen expression, antigenic modulation and development of human antimouse antibodies. Wilder et al. further teach the importance of dosimetry for treatment planning and assessment of results, wherein dosimetry is dependent on the kinetics of uptake and clearance of radiolabeled antibodies, the distribution of radiolabeled antibodies and the radioisotope attached to the antibody (page 1387, 1st column, 3rd paragraph from bottom). For example, Wilder et al. teach that the transport of antibodies through the intestinal space of a tumor by diffusion and convection is impeded by antigen binding and relatively large extravascular distances which results in a heterogeneous distribution of antibodies. Along the same lines, Erdi et al. (Phys. Med. Biol. 1996; 41: 2009-20026) disclose that although RIT (radioimmunotherapy) is an innovative and promising approach, there is problems to be solved which limit its use (page 2009, Introduction). These problems include: (1) the low uptake of the radiolabeled antibody; (2) the low target:non-target ratios and the inhomogenous distribution of antibodies within the tumor. While these reference demonstrate the importance of the specificity, uptake and distribution of the antibody in radioimmunotherapy, the same consideration and/or problems associated with RIT are found with radio imaging as well, see for example Chatel et al. (Eur. J. Nucl. Med. 1992; 19: 205-213). As such, in view of the teachings of Mason et al, supra, the skilled artisan would not have found sufficient guidance in the specification to achieve an effective method of treating an/or imaging tumors comprising administering any and/or all radiolabeled antibodies to melanin.

In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

In response to this rejection, Applicants assert that the articles cited by the Examiner are directed to the general field of radioimmunotherapy and radioimaging and do not specifically address therapy and imaging of melanin-containing tumors. In particular, Applicants contend that while Wilder et al. (1996) disclose several challenges that currently face radioimmunotherapy, Wilder et al. discloses several solutions to each of these concerns which are also relevant in regard to the presently claimed invention, see Table 4 on page 1393. For example, Applicants assert the following: 1) circulating free antigen should not raise a problem for imaging or treating the tumor because the greatest concentration of free melanin is expected to be in the tumor and its immediate vicinity from dead or dying tumor cells; 2) in contrast to conventional tumor antigens, melanin is expected to be sequestered by macrophages in the liver and spleen becoming intracellular and not accessible to antibodies that cannot be internalized by the cell; 3) antibodies do not have to penetrate the tumor cells to be effective for therapy or imaging since antibodies can bind to melanin from dead or dying tumor cells and/or the antibody can gain access to melanin in the cells following disruption of the cell membrane; 4) efficacy of treatment may increase with subsequent cycles because adjacent cells can be killed by the radiation even if the tumor cells do not contain melanin, wherein more melanin would be expected to accumulate in the tumor as a result of the tumor cells being killed. Moreover, as noted by Wilder et al. (Fig. 2), antibodies can be "humanized" to prevent possible development of human antibodies. In this regard, Applicants assert that the U.S. Food and Drug Administration has approved several humanized antibodies for the treatment of cancer in human subjects, including, for example, Herceptin, Erbitux, Rituzan, Mylotarg, Campath and Avastin. Applicants further assert that since the publication of the 1954 research report by Mason et al. and the 1992 (Chatel et al.) and 1996 (Wilder et al.; Erdi et al.) review articles cited by the Examiner, radioimmunotherapy has advanced by a quantum leap as evidenced, for example, by the attached 2004 review article by Milenic et al. (Nature Rev. Drug Discovery 3: 488-498, 2004) which concludes with "after more than two decades, mAb-targeted therapies are generally recognizes as making a significant impact on cancer therapy." In addition, Applicants assert that the present invention represents a major advance in the treatment of melanoma, wherein the last drug to treat melanoma was approved by the FDA 30 years ago. Finally, Applicants contend that even if the

invention as claimed did read on an inoperative embodiment, "the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that the articles cited by the Examiner are directed to the general field of radioimmunotherapy and radio-imaging and do not specifically address therapy and imaging of melanin-containing tumors, the Examiner acknowledges that the articles represent the general field of radioimmunotherapy and radio-imaging. However, the Examiner recognizes that many of these "limitations" discussed above extend beyond a particular type of cancer and are applicable to melanin containing tumors. Regarding Applicants assertion that these "limitations" have been overcome by the instant invention and/or are not applicable to melanin-containing tumors, the Examiner acknowledges that Applicants have asserted what "should be expected to" or "would be expected to" occur in melanin antibody targeting and/or treatment of melanin containing tumors. However, the Examiner recognizes that Applicants appear to be providing an opinion of what should happen or what would be expected to happen without providing any factual evidence as to any outcome. Thus, it would require undue experimentation to practice the invention as claimed in view of the state of the prior art for radioimmunotherapy and radio-imaging as discussed above. Regarding the cited Milenic et al. reference, the Examiner acknowledges that Milenic et al. concludes with "after more than two decades, mAb-targeted therapies are generally recognizes as making a significant impact on cancer therapy." However, the Examiner recognizes that in the next paragraph Milenic et al. states "[H]owever, despite the wealth of knowledge and capability in antibody engineering, the first two approved radiolabelled mAbs were murine in nature and subject to all of the resultant limitations; that is, immunogenicity and biological half-lives. Knowledge of actual clinical use of radiolabelled mAbs remains in its infancy in many respects, particularly with regards to therapies beyond lympho-haematological diseases, fractionated dosing and the rational construction of drug-combination cocktail therapies to functionally integrate targeted radiation therapy with established therapies and external beam therapies." Thus, the 2004 article by Milenic et al. appears to support the unpredictability of radioimmunotherapy. Lastly with respect to Applicants

arguments pertaining to inoperative embodiments, the Examiner acknowledges that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. However, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1/18/2007

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